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Research report

Different effects of running wheel exercise and skilled reaching training on corticofugal tract plasticity in hypertensive rats with cortical infarctions

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ABSTRACT

The approaches that facilitate white matter plasticity may prompt functional recovery after a stroke. The effects of different exercise methods on motor recovery in stroke rats have been investigated. However, it is not clear whether their effects on axonal plasticity different. The aim of this study was to compare the effects of the forced running wheel exercise (RWE) and skilled reaching training (SRT) on axonal plasticity and motor recovery. Cortical infarctions were generated in stroke-prone renovascular hypertensive rats. The rats were randomly divided into the following three groups: the control (Con) group, the RWE group, and the SRT group. A sham group was also included. The mNSS and forelimb grip strength tests were performed on days 3, 7, 14, 21, 28, 35, and 42 after ischemia. The anterograde tract tracer biotinylated dextran amine (BDA) was injected into the rats to trace the axonal plasticity of the contralesional corticofugal tracts. Compared with the Con group, the mNSS scores in the SRT and RWE groups decreased on day 28 ($P < 0.05$) and on days 35 and 42 ($P < 0.01$). The grip strength in the SRT group increased relative to that in the RWE group at 42 day post-ischemia ($P < 0.01$). Both the RWE and SRT groups exhibited enhanced plasticity of the contralesional corticofugal tract axons at the level of the red nucleus ($P < 0.01$) and the cervical enlargement ($P < 0.01$). More contralateral corticorubral tract remodeling was observed at the red nucleus level in the SRT group than in the RWE group ($P < 0.001$). Taken together, these results suggest that SRT may enhance axon plasticity in the corticorubral tract more effectively than the forced RWE and is associated with better motor recovery after cerebral ischemia.

1. Introduction

Stroke is the leading cause of adult disability worldwide, and the subsequent functional rehabilitation remains a major challenge for rehabilitation teams. As shown in recent studies, the infarct volume does not play a major role in motor dysfunction [1]. Instead, the pyramidal tract injury per se and the subsequent degeneration are closely related to the motor deficits after stroke [2]. Secondary anterograde degeneration occurs in remote non-ischemic brain areas, including the ipsilateral thalamus, the striatum, and the distal pyramidal tract, which are synaptically connected with the primary lesion [3,4]. Secondary degeneration is well characterized by diffusion tensor imaging (DTI) and is manifested as decreased fractional anisotropy (FA) in the pyramidal tract and other pathways [5]. As reported by an increasing number of studies, the more extensive the degeneration is, the poorer the grip strength and hand dexterity are, and the greater the level of physical impairment is [2,6,7].

Currently, the mechanism underlying motor recovery is not clear. Rong et al. [8] reported that the degree of degeneration and compensation by the spared *peri*-infarct corticospinal tract might be an important mechanism for motor recovery, whereas Liu et al. [9] showed that axons from the contralesional motor cortex sprouted into the denervated spinal cord after a stroke and might contribute to functional recovery after stroke. No matter which side is more important, since plasticity of the white matter tract occurs in all stages of stoke, including the acute, sub-acute, and chronic stages [3], therapies intended to alleviate axonal degeneration or promote axonal regeneration to improve functional recovery after stroke seem to have wide therapeutic time windows.

Interventions that prompt corticofugal tract remodeling have been explored to enhance functional recovery following stroke, including erythropoietin, human stem cells, a monoclonal antibody against IN-1(a

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monoclonal antibody of recombinant Nogo-A), and constraint-induced movement therapy [10–13]. Because axonal reorganization responds to and is shaped by activity, physical exercise potentially has an influence on axonal rewiring post-stroke [11,14]. Improved behavioral recovery after constraint-induced movement therapy is partially associated with enhanced post-stroke axonal growth and synaptic plasticity [15].

Previous studies have indicated that the influences of different physical training approaches on neurological function recovery vary. Each type of physical training pattern has merits and limitations [16–18]. Physical exercise focuses on motion, particularly locomotor activity, whereas physical training consists of skilled motor tasks. Both methods exert different effects on structural and/or functional recovery in intact and brain-damaged animals [18]. In the study by Maldonado et al. [16], motor skill training was more effective than voluntary running exercise in promoting skilled reaching recovery in the sensorimotor cortices of ischemic rats, although the underlying mechanism was not explored.

The hypothesis of this study was that physical training and physical exercise would promote different effects on the plasticity of the corticofugal tract after focal cerebral ischemia. The aims of this study were to compare the effects of forced running wheel exercise (RWE) and skilled reaching training (SRT) on motor function recovery and corticofugal tract remodeling in rats with cortical ischemia.

2. Material and methods

2.1. Experimental design

The study timeline was illustrated in Fig. 1. All of the rats were pretrained on skilled reaching for 2–3 weeks prior to middle cerebral artery occlusion (MCAO) in the feeding cages (as shown in Fig. 2A). During the last three days of pre-training, the rats underwent individual training in the single pellet-reaching box (as shown in Fig. 2B) for 30 min per day to acquaint them with the reaching box used in the post-operative training. Those rats with success rates of more than 60% on the reaching task performed on the last day of pre-training were selected for MCAO surgery. The different physical training methods began 3 days after MCAO. The behavioral tests were assessed on days 3 and 7 and weekly thereafter until 42 days post-MCAO. The tract tracers were injected on day 42.The rats were sacrificed two weeks later.

2.2. Animals

2.2.1. Stroke-prone renovascular hypertensive model

90 male Sprague Dawley rats (3–4 weeks) weighing 60–90 g were used to establish stroke-prone renovascular hypertensive model (RHRSP) as previously described [19]. All of the animals were deeply anesthetized with 10% chloral hydrate (3 ml/kg body weight). Systolic blood pressure was measured in preheated (60 °C, 15 min) conscious rats after bilateral renal artery constriction twice per week for 12 weeks using an indirect tail-cuff sphygmomanometer (China-Japan Friendship Hospital, Beijing, China). Next, 59 rats weighing 300–450 g with systolic blood pressures higher than 180 mm Hg and without stroke symptoms were selected for the pre-MCAO training. The rats were housed socially (3–4 rats/cage) in the same animal care facility on a 12-h light/dark cycle throughout the experiment.

2.2.2. Pre-MCAO training

Two to three weeks prior to the MCAO, all of the RHRSP rats received skilled reaching pre-training, which included group training and individual training. In group training, 3–4 rats were trained together in their feeding cages. A railing with 1-cm gaps was placed in each feeding cage. The rats were able to access food pellets (approximately 45 mg) through the gaps in the railing (Fig. 2A). During the last three days of pre-training, the rats underwent individual training in the single pellet-reaching box (Fig. 4B) for 30 min per day to acquaint them with the reaching box used in post-operative training. Each rat was individually trained in a Plexiglas chamber (34cm × 14 cm × 29 cm) with a slit (10 mm) in the center of the front wall. A 5cm × 3.5 cm Plexiglas shelf was attached to the outer front wall in front of the slit at a height of 3 cm above the floor of the chamber, which was fixed to the left or right side of the slit according the preferred limb. One food pellet was placed on the shelf located contralateral to the preferred limb at a distance of 1 cm from the reaching window during each training session. The floor of the training box was composed of metal rods through which the lost pellets fell to prevent the rats from retrieving the pellets that fell inside the box. On the last day of pre-training, the preferred limb and the success rates were recorded. If the rat successfully reached the food and consumed it, the attempt was recorded as “successful”; otherwise, the attempt was recorded as “unsuccessful”. Only the rats with success rates on the reaching task of up to 60% were randomized into the MCAO or sham groups. Indeed, 46 rats that had success rates of more than 60% (approximately asymptotic performance) on the reaching task were selected for the MCAO or sham operations. The preferred-for-reaching forelimb, namely, the limb that was used to reach the food pellets 20 consecutive times over a 10-min session [16], was recorded. Among which 13 rats who failed to learn how to access food through the aperture at the end of pre-MCAO training were withdrawn from further study.

2.3. MCAO surgical procedures

46 RHRSP rats (15–16 weeks) were assigned randomly to receive focal cortical infarction (n = 36) or sham MCAO surgery procedures (n = 10) as described previously [4,19]. Briefly, the rats were deeply anesthetized with 10% chloral hydrate (3.5 ml/kg body weight). The right or left (contralateral to the preferred-for-reaching limb) middle cerebral artery (MCA) was exposed and then occluded at the distal segment, which was approximately the origin of the striatal branches, using bipolar electrocoagulation, which resulted in a permanent focal infarction in the neocortex. In the sham-operated animals (n = 10), the MCA was only exposed but not occlusion.

Neurological function was evaluated 6 h after MCAO using Bederson’s neurological function test [20]. The Bederson’s scores were evaluated according to the following criteria: no deficits, score of 0; unable to extend the contralateral forelimb, score of 1; flexion of the contra-lateral forelimb, score of 2; mild circling to the contra-lateral side, score of 3; and severe circling and allying to the contra-lateral side, score of 4.

Two rats with scores of 4 according to the Bederson’s scores [20]

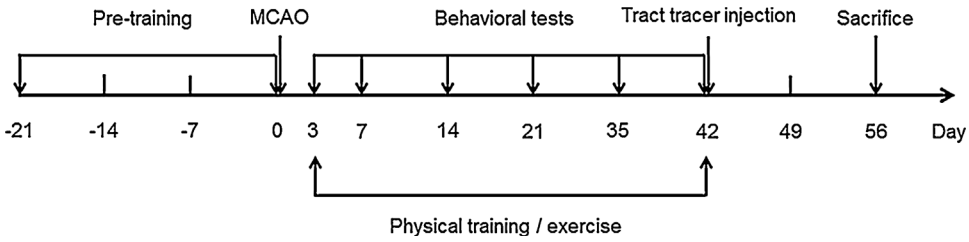

Fig. 1. Experimental design. The arrows indicate the timing of pre-training, middle cerebral artery occlusion (MCAO), behavioral tests, different physical training methods (forced running wheel exercise and skilled reaching training), tract tracer injection, and sacrifice. The physical training began on day 3 after stroke and continued until day 42.